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Review

Resting-state functional reorganization in Parkinson's disease: An activation likelihood estimation meta-analysis

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ABSTRACT

Parkinson's disease (PD) is a common progressive neurodegenerative disorder. Studies using resting-state functional magnetic resonance imaging (fMRI) to investigate underlying pathophysiology of motor and non-motor symptoms in PD yielded largely inconsistent results. This quantitative neuroimaging meta-analysis aims to identify consistent abnormal intrinsic functional patterns in PD across studies. We used PubMed to retrieve suitable resting-state studies and stereotactic data were extracted from 28 individual between-group comparisons. Convergence across their findings was tested using the activation likelihood estimation (ALE) approach. We found convergent evidence for intrinsic functional disturbances in bilateral inferior parietal lobule (IPL) and the

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supramarginal gyrus in PD patients compared to healthy subjects. In follow-up task-based and task-independent functional connectivity (FC) analyses using two independent healthy subject data sets, we found that the regions showing convergent aberrations in PD formed an interconnected network mainly with the default mode network (DMN). Behavioral characterization of these regions using the BrainMap database suggested associated dysfunction of perception and executive processes. Taken together, our findings highlight the role of parietal cortex in the pathophysiology of PD.

1. Introduction

Parkinson's disease (PD) is a common progressive neurodegenerative disorder, which affects more than seven million people globally (Willis, 2013; de Lau & Breteler, 2006). It has been demonstrated that functional and structural loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) leads to fundamental alterations in basal ganglia circuits. Involvement of cortical and subcortical brain areas and other neurotransmitter changes (e.g., cholinergic or serotonergic systems), however, also contribute substantially to PD symptoms (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004; Del Tredici, Rub, De Vos, Bohl, & Braak, 2002). PD is clinically characterized by progressive motor features such as bradykinesia, rigidity, resting tremor and postural instability (Braak et al., 2003; Jankovic, 2008). In addition, several studies highlighted the relevance of non-motor symptoms including depression, cognitive impairment, anxiety, sleep disorders, and impulsive behavior in PD (Chaudhuri, Healy, Schapira, & National Institute for Clinical, 2006). These symptoms are contributing to a severe disability and inevitably lead to a decreased quality of life of PD patients. However, their neuroanatomical and neurochemical substrates are still poorly understood.

To assess the neural correlates of motor and non-motor symptoms in PD, numerous functional neuroimaging studies localized and quantified abnormalities within and between different brain regions (cf. Eckert, Tang, & Eidelberg, 2007; Prodoehl, Burciu, & Vaillancourt, 2014; Stoessl, 2009; Tahmasian, Bettray, et al., 2015). Task-based functional magnetic resonance imaging (fMRI) has been used in many studies over the last two decades to assess aberrant recruitment of brain regions in the context of experimental paradigms using a subtraction approach between a target and a control condition (Herz, Eickhoff, Lokkegaard, & Siebner, 2014; Rana, Masroor, & Khan, 2013; Rottschy, Kleiman, et al., 2013). However, these task-based designs are strongly influenced by compliance and task performance of subjects, which might have confounded the results.

As an alternative approach, resting state fMRI (rs-fMRI) has been widely applied over the last decade in healthy populations and various neurodegenerative and neuropsychiatric disorders (Biswal, 2012; Khazaie et al., 2017; Klupp et al., 2015; Meng et al., 2014; Pasquini et al., 2014; Riedl et al., 2014; Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Tahmasian et al., 2013; Tahmasian, Pasquini, et al., 2015; Tahmasian et al., 2016). Rs-fMRI is based on fluctuations of the blood-oxygen-level dependent (BOLD) signal that are associated with the intrinsic neuronal activity of the brain, while subjects are in the awake state without performing any specific task, i.e., in an endogenously controlled state of mind-wandering (Biswal, 2012; Fox, Snyder, et al., 2005; Snyder & Raichle, 2012). In contrast to task-related fMRI, rs-fMRI substantially reduces the potential influences of compliance and task performance (Di Martino et al., 2008). There is a rich literature evaluating intrinsic functional disturbances in PD using different rs-fMRI analysis methods, including seed-based functional connectivity (FC), independent component analysis (ICA), regional homogeneity (ReHo), amplitude of low frequency oscillations (ALFF), and graph analysis under different medication states (for review see: Prodoehl et al., 2014; Tahmasian, Bettray, et al., 2015).

Previously, we summarized the current rs-fMRI literature in PD and suggested that seed-based FC and effective connectivity are valuable techniques for assessing the disruption of connectivity between specific brain areas, while network-based and graph analysis methods are promising approaches for assessing functional alterations across the whole brain. ReHo and ALFF can also be applied to study local intrinsic abnormalities in PD. In addition, we concluded that dopamine replacement therapy induces functional reorganization of the brain and normalizes functional alterations in PD (Tahmasian, Bettray, et al., 2015). Despite above-mentioned advantages, the previous rs-fMRI studies point to diverse and often conflicting findings. One reason for this predicament seems to be the variety of rs-fMRI preprocessing (e.g., different normalization, motion correction, and global signal regression) and analyzing strategies. Seed-based methods measure FC between the averaged BOLD time course of a region of interest (ROI) (or a seed) and the time course of other brain voxels; ICA is a data-driven approach that identifies intrinsic neural networks; ALFF, as a regional approach, assesses the regional intensity of oscillatory fluctuations in the BOLD signal; ReHo is also a regional method, which calculates the similarity between the BOLD signal of particular voxels and the nearest voxels within a given cluster. Thus, ReHo and ALFF are conceptually different pertaining to connectivity because they investigate local phenomena. The link between the different aspects of resting state physiology is still not clarified yet. Thus, in order to characterize resting state abnormalities in PD as comprehensively as possible we included findings from all approaches. Of note, we excluded seed-based FC studies because such analyses entail a strong prior selection-bias in